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# Predicting the onset of major depression in subjects with subthreshold depression in primary care: a prospective study

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**Objective:** That subjects with subthreshold depression have an increased probability of developing major depression has been confirmed by many studies. However, the factors which may predict the onset of major depression have yet to be fully examined.

**Method:** We examined the control group of a randomized trial in primary care patients with subthreshold depression ( $N = 109$ ), of whom 20 had developed major depression 1 year later. Using the vulnerability-stress theory, we examined which factors predicted the onset of major depression.

**Results:** In both univariate and multivariate analyses, family history and chronic illnesses predicted the onset of major depression.

**Conclusion:** It is possible to predict to a certain degree whether a subject with subthreshold depression will develop major depression within a year.

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Key words: depressive disorder; incidence; prospective studies; primary health care; risk factors

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## Introduction

Subthreshold symptoms of depression may consist of three types of symptoms (1): prodromes, predicting the onset of an episode of major depression; residual symptomatology after recovery from an earlier episode; or the depressive symptoms may constitute an independent condition, such as minor depression as defined in the DSM-IV, or recurrent brief depression, which are not definitely considered to be a diagnostic category. It is, however, not yet possible to distinguish these three types of subthreshold depression in a reliable way. When a subject presents himself with subthreshold depression (without meeting diagnostic criteria for major depression), for example in primary care, it can be established with a diagnostic interview whether that person had an earlier depressive episode. But, there is only limited evidence that can be used to predict whether this subject will develop a major depression in the near future or not.

It is on the other hand well established that depressive symptoms that do not meet the criteria for major depression, are an important precursor

of major depression. The incidence rate of major depression in subjects with subthreshold depression in community studies ranges from 0.01 to 0.15 new cases per 100 person years, compared with 0.00 to 0.05 in subjects without subthreshold depression (2–6). In studies among medical patients with subthreshold depression the incidence rates range from 0.06 to 0.58, compared with 0.00 to 0.23 in subjects without subthreshold depression (7, 8). Virtually all of the many studies that have examined the incidence rates of major depression in subjects with subthreshold depression compared with those without, confirm that the incidence rate is greatly increased in subthreshold depression (2).

However, which subjects with subthreshold depression will develop a major depression, and which will not, has hardly been examined. Most studies focus on the question whether subjects with subthreshold depression do indeed have an increased risk of getting major depression. The few studies that focus on the risk of getting major depression among subjects with subthreshold depression indicate that subjects with feelings of guilt or worthlessness more often get major depression than other subjects with subthreshold

depression (9, 10). There are also some indications that the number of depressive symptoms is related to the onset of major depression (9), as well as the presence of concentration problems (11). None of the studies until now has focused on more general risk factors for getting major depression among subjects with subthreshold depression, such as vulnerability, coping skills, family history of depression, suspiciousness (12), or life events (13).

The question which subjects with depressive symptoms do get major depression and which do not, is, however, an important research question, both from a scientific point of view and from a clinical point of view. Scientifically, this question is important because it may increase our understanding of the process by which an individual develops MDD and of the role of depressive symptoms in the process. From a clinical point of view, a reliable assessment of the risk for getting major depression can be an important tool for the development of interventions aimed at the prevention of major depression. Several recent studies in this area have found evidence that it is indeed possible to reduce the number of new cases of MDD by intervening in subjects with subthreshold depression (14–16).

#### Aims of the study

To examine the incidence of major depression in a population with subthreshold depression, selected from general practice and the variables predicting the onset of major depression.

### Material and methods

#### Respondents

The respondents from this study constituted the control group of a randomized trial of an intervention aimed at preventing the onset of major depression in primary care patients with subthreshold depression. We recruited patients from 19 general practices in the Netherlands. Patients were eligible if they were aged between 18 and 65 years, gave written informed consent to participate in the trial, and had current depressive symptoms (according to the Instel, described below) not meeting DSM-IV criteria for a depressive disorder. Patients were excluded if they had hearing or language difficulties, received psychological treatment by a mental health professional in the last year, were on the waiting list for treatment, suffered from a life-threatening illness, mental retardation, suicidal risk, psychotic symptoms, schizophrenia or dementia, or if they met DSM-IV criteria for depressive disorder, dysthymia,

bipolar disorder, social phobia, agoraphobia or panic disorder in the last 12 months.

Participants were recruited in two steps. In the first step, a research assistant approached all patients who were waiting to see their GP ( $N = 5276$ ). The Instel-screen (17) was used as a screener during a brief face-to-face interview in a separate room. This instrument has been developed for use in primary care to detect major depression and generalized anxiety disorder. At a cut-off of one core symptom and three depressive symptoms, the positive predictive value was 56% and the specificity 97%.

Of the 4525 patients who gave informed consent for screening, 3825 patients were screened. The remaining 700 patients were excluded on the basis of age or exclusion criteria as cited above. In total, 1018 patients were assessed as having subthreshold depression according to the Instel questionnaire. In the second step, screen-positive patients who were willing to participate in the trial received a telephone interview to establish the presence of major depression: the Composite International Diagnostic Interview [CIDI-Auto version 2.1 (18), Dutch version] (19). This resulted in 363 baseline interviews. Patients who met DSM-IV diagnostic criteria for a mood disorder, social phobia, agoraphobia or panic disorder in the last 12 months were excluded ( $n = 95$ ). Patients meeting all inclusion criteria and who gave informed consent, were randomized to the intervention (minimal contact psychotherapy;  $n = 107$ ) or to usual care ( $n = 109$ ). One year later, the CIDI was conducted once more in order to examine how many of the subjects had developed a major depression in the past year.

This study is limited to the 109 subjects who received usual care. For this study, we used the data collected at baseline ( $t_0$ ) and 1 year later ( $t_1$ ). Twenty of the 109 subjects (18%) went on to develop a major depression during the following year.

Most subjects were female (66.1%), lived with a partner (75.2%), had a paid job (75.2%), had no relative (parent, sibling) with a history of depression (64.2%), had not experienced a major life event in the past year (59.6%), and most had at least one physical illness (77.1%; mean number of illnesses was 1.82;  $SD = 1.67$ ). The mean age was 41.83 years ( $SD = 11.24$ ), and the mean score on the CES-D was 13.01 ( $SD = 8.48$ ; 29.4% scored above the cut-off score of 16).

#### Theoretical model

As a general model for understanding the process by which a subject develops a depressive disorder,

we used the vulnerability-stress theory of Brown and Harris (20). This model states that a depression is caused by a combination of physical, psychological and social factors. Subjects who suffer a depressive disorder have a physical vulnerability, but develop a disorder when they are confronted with situational, emotional or physical stressors. This model was empirically supported in several cultural settings (21). In the current study, we used the basic elements of this model that were included as measurement instruments in the randomized trial.

#### Measurement instruments

*Subthreshold depression.* As a screen for subthreshold depression, the Instel-screen was used (17). This instrument has been developed for use by GPs to detect major depression and generalized anxiety disorder. To assess the optimal cut-off point for subthreshold depression, secondary analyses were performed. At a cut-off of one core symptom and three depressive symptoms the positive predictive value was 56% and the specificity 97%.

*Major depression.* The presence of major depression and other mental disorders (at  $t_0$  for exclusion, and at  $t_1$  for examining the incidence of major depression during the past year) was established with the CIDI-Auto (computerized version). The CIDI is a standardized diagnostic interview for the assessment of mental disorders, developed by the World Health Organization. It was designed for use by trained interviewers who are not clinicians. Its reliability has been demonstrated to be good to excellent and the validity has been demonstrated to be adequate (22, 23). The interviews were carried out by telephone, by interviewers who received a 3-day training at the Dutch WHO-CIDI training center, followed by 1-day training in adhering to the interview protocol.

*Level of depressive symptomatology.* The level of depressive symptomatology at  $t_0$  was measured using the Center for Epidemiological Studies Depression Scale [CES-D (24), Dutch version (25)], a widely used self-report scale consisting of 20 questions about the presence of depressive symptoms during the past week. The CES-D generates a total score that can range from 0 to 60, with a higher score indicating more depressive symptoms. The Dutch translation has good reliability and validity (25). The CES-D data were collected by telephone at baseline and at follow-up (together with the CIDI-interview).

*Depression in the family.* As an indication of inherited vulnerability, we asked respondents to indicate whether their father, mother, brother, or sister had ever suffered from depression. We made a dichotomous variable, indicating the presence or absence of depression in the family.

*Personality characteristics.* We used the NEO-FFI Personality Inventory (26), Dutch version (27), as a profile of the personality of the respondents. Personality traits can be considered to be an element of the psychological vulnerability. The NEO-FFI consists of 60 statements about the personality, and for each statement the respondent should indicate on a five-point scale how much this is applicable to the subject. The NEO-FFI has five subscales or dimensions: altruism, conscientiousness, extraversion, neuroticism, and openness.

Life events in the past year were measured with the List of Threatening Experiences (LTE-Q), the Dutch version (28, 29). This list consists of 12 categories of common life events that are highly likely to be stressful, such as suffering from a serious illness or having a major financial crisis. In a psychiatric population, the LTE-Q was shown to have high test-retest reliability, good agreement with informant information and both high specificity and sensitivity (30). For the purposes of our study, we subdivided some categories into different items, resulting in 17 items. As no underlying assumptions were made about the inter-relationship of individual life events, Cronbach's alpha values were not calculated.

The presence of chronic illnesses was assessed by asking the respondents whether they had one of the most common 24 chronic illnesses at baseline (31). Demographic variables used in this study were: gender, age, living with or without a partner, and having a paid job.

#### Analyses

First, we examined the differences between the subjects who had developed major depression at 12-month follow-up and subjects who had not, in univariate analyses. We conducted a series of logistic regression analyses, with the development of major depression (yes/no) as the dependent variable, and each of the variables described in Table 1 as predictors.

Secondly, we conducted another logistic regression analysis, with the development of major depression (yes/no) as the dependent variable. But this time, we entered all the variables that

	Univariate analyses	Multivariate analyses†	Multivariate analyses‡
Gender	1.02 (0.98–1.08)	–	1.02 (0.94–1.10)
Age	1.01 (0.96–1.05)	–	1.02 (0.95–1.08)
Living with partner	0.99 (0.32–3.02)	–	1.53 (0.28–8.46)
Paid job	2.09 (0.56–7.78)	–	4.29 (0.59–31.16)
Life events in past year ( <i>N</i> )	1.06 (0.68–1.63)	–	0.70 (0.34–1.42)
Chronic illnesses ( <i>N</i> )	3.36 (1.12–10.03)*	1.60 (1.13–2.25)**	2.00 (1.30–3.07)**
Family history of depression	4.50 (1.61–12.56)**	4.48 (1.30–15.47)*	5.18 (1.24–21.66)*
CES-D at <i>t</i> <sub>0</sub>	1.10 (1.03–1.16)**	1.07 (0.99–1.15)	1.13 (1.01–1.25)*
Personality			
Altruism	1.11 (0.86–1.43)	–	1.19 (0.81–1.74)
Conscientiousness	1.02 (0.77–1.36)	–	1.43 (0.92–2.21)
Extraversion	0.87 (0.67–1.13)	–	1.12 (0.71–1.75)
Neuroticism	1.53 (1.10–2.14)*	1.19 (0.80–1.77)	1.32 (0.83–2.09)
Openness	1.05 (0.80–1.37)	–	1.20 (0.79–1.83)

†Logistic regression analysis with the four variables that were found to be significant in the univariate analyses, as predictors.

‡Logistic regression analysis with all variables as predictors.

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

Values are presented as odds ratios (95% confidence intervals) unless indicated. *N* = number of items.

Table 1. Predictors of onset of major depression in subjects with subthreshold depression in univariate and multivariate analyses

were found to be significant in the univariate analyses, into the regression analysis as predictors.

Thirdly, we conducted a logistic regression analysis with the development of major depression (yes/no) as the dependent variable and all variables from Table 1 together as predictors.

Finally, we explored which combinations of significant predictors of major depression predicted most cases of major depression, and calculated the sensitivity, specificity, positive predictive value, and negative predictive value of significant predictors. For these analyses we first dichotomized the continuous outcomes (CES-D above/below cut-off of 16; two or more chronic illnesses vs. 0 or 1). Each prognostic variable had a score of 0 or 1. For each of these prognostic variables, and for each combination of these variables, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value for predicting the onset of major depression.

The analyses were conducted in SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Specificity, sensitivity, positive and negative predictive value were calculated according to the formulas described by Sacket et al. (32).

## Results

### Univariate analyses

In the univariate analyses, four variables at baseline were found to be significantly related to the onset of major depression at follow-up (Table 1): a family history of depression ( $P < 0.01$ ); the number of chronic illnesses ( $P < 0.05$ ); the level of depressive symptoms as indicated with the CES-D ( $P < 0.01$ ); and neuroticism ( $P < 0.05$ ).

### Multivariate analyses

We conducted a logistic regression analysis with the onset of major depression (yes/no) as the dependent variable and the four variables that were found to be significant in the univariate analyses, as predictors (Table 1). Only two of the variables remained significant: the number of chronic illnesses ( $P < 0.01$ ), and family history ( $P < 0.05$ ).

Then we entered all variables together as predictors in a logistic regression analysis, and found three variables to be significant: the number of chronic illnesses ( $P < 0.01$ ), family history ( $P < 0.05$ ), and the CES-D score ( $P < 0.05$ ).

### Risk profiles and prognosis

We decided to examine the three possible prognostic variables or risk indicators for developing major depression at follow-up that were found in the last regression analysis in which all variables were entered together as predictors: the number of chronic illnesses, the level of depressive symptoms at baseline (CES-D score), and a family history of depression. We wanted to explore the possibilities of using these variables for predicting the onset of major depression in individual subjects (Table 2).

The negative predictive value of the prognostic variables and their combinations is fairly high, indicating that subjects not scoring positively on one of these variables, have a low chance of developing major depression at follow-up. The negative predictive values of the combinations of prognostic variables are not higher than those of the singular variables. The positive predictive values of the variables and their combinations

Table 2. Sensitivity, specificity, positive predictive value, and negative predictive value of risk factors and combinations of risk factors for major depression

	Inc of MDD		SENS	SPEC	PPV	NPV
	+	–				
Family history of depression						
+	13	26	0.65	0.71	0.33	0.90
–	7	63				
≥2 chronic illnesses						
+	15	42	0.75	0.53	0.26	0.90
–	5	47				
CES-D score ≥16						
+	10	22	0.50	0.75	0.31	0.87
–	10	67				
Family history + ≥2 chronic illnesses						
+	12	20	0.60	0.78	0.38	0.90
–	8	69				
Family history + CES-D score ≥16						
+	8	10	0.40	0.89	0.44	0.87
–	12	79				
≥2 chronic illnesses + CES-D score ≥16						
+	9	21	0.45	0.76	0.30	0.86
–	11	68				
Family history + ≥2 chronic illnesses + CES-D score ≥16						
+	7	6	0.35	0.93	0.54	0.86
–	13	83				

Inc, incidence; MDD, major depressive disorder; SENS, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value.

were found to be rather low. The sensitivity of each of the variables and their combinations was moderate. The specificity was moderate for all of the variables and the specificity of the combinations of variables was also moderate.

## Discussion

This study has several limitations. First, the subjects included in this study may not be representative of the total population of primary care patients with subthreshold depression, as we used subjects from the control condition of a randomized controlled trial of minimal contact psychotherapy and applied stringent selection criteria. On the other hand, this population had agreed to participate in a randomized trial and may therefore be representative of primary care patients willing to accept a preventive intervention. The results of this study can therefore possibly be generalized to a larger population in primary care. Secondly, the number of subjects developing major depression at 1-year follow-up was relatively small ( $N = 20$ ). On the other hand, this small number could have easily resulted in no significant predictor of major depression. Therefore, the predictors we found to be significant can be considered to be very strongly related to the onset of major depression. Thirdly, we examined only a selection of relevant risk factors. For example, we did not examine whether

the subjects had a history of major depression beyond the past 12 months before baseline, while it is very likely that earlier depressive episodes are an important predictor of new episodes.

On the other hand, we did find clear indications as to which subjects with subthreshold depression will develop major depression and which will not. First, we found that family history of depression is a prognostic variable for the onset of major depression. Secondly, the presence of chronic physical illnesses is related to the onset of major depression. This is a confirmation of the results of a large body of research indicating that chronic illnesses may cause, directly or indirectly, the onset of major depression (33). Thirdly, there was a suggestion that a higher level of depressive symptomatology predicted the onset of major depression. This seems quite plausible, indicating that when depressive symptoms become more serious, the chance that they will develop into a major depression increases. It is also in agreement with earlier research (9).

In general, these results are in agreement with the vulnerability-stress theory of Brown and Harris (20). These above predictors of major depression have a central place in this model with family history as an important aspect of vulnerability, and chronic illness as a stress factor. The severity of depressive symptomatology may be considered to be an indicator of the position in the process leading to major depression.

We also examined whether these prognostic variables could be used in predicting the onset of major depression in individual subjects. These analyses showed that these variables cannot be used in individual patients to predict whether they will get a major depression or not. The sensitivity and positive predictive value were too low for that. The negative predictive value, however, was quite considerable, indicating that when these prognostic variables are negative, up to 90% of the cases will not develop a major depression. And this was true for each of the variables alone. This suggests that when a subject does not have a family history of major depression or has less than two chronic illnesses, the chance that he or she will develop major depression is only 10%.

Perhaps the most important finding of this study is that it is possible to predict to a certain degree whether a subject will develop major depression when exposure to a small number of key variables is known. As the process of developing major depression is as yet poorly understood, it is important to replicate this study with a larger and more representative population, and with a more comprehensive set of putative prognostic

factors. The results of this study indicate that such a study could considerably enhance our understanding of that process.

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